REMARKS

This is in response to the Office Action mailed on January 9, 2007.

Claims 30-34 have been added and claims 6 and 22 have been cancelled without prejudice to their prosecution in another case. Accordingly, claims 2, 4, 8-10, 24-33 and 34 are now pending in the application.

Support for the subject matter of new claim 30 relating to specific types of photosensitizers can be found throughout the application and claims as originally filed, for example, at page 12, lines 11-24.

Support for the subject matter of claims 31-34 can also be found throughout the application and claims as originally filed. For example, the subject matter of claims 31-34 is supported by specification at page 13, lines 6-9.

Claims 2, 4, 9, 24 and 26 are amended. In particular, the phrase "presenting" an antigenic peptide has been used in the first line of claims 2 and 24 (rather than "expressing" an antigenic molecule) and dependent claims 4, 9 and 26 have been amended to harmonize the language in this regard. Support for use of presentation of an antigenic peptide can be found throughout the specification, for example, at page 7, line 3 to page 8, line 30; Examples 1, 2 and 3 as originally filed (see also, page 7, lines 17-18). In addition, reference to certain photosensitizing agents and MHC II has been deleted from claim 1. Also, the phrases to generate "a cytotoxic T cell" response and "cytotoxic T cell mediated cell killing" have been used in claim 1 (rather than language relating to an immune response). Support for cytotoxic T cell responses and cytotoxic T cell mediated cell killing, can be found throughout the specification, for example, at page 9, line 15 to page 10, line 28; page 11, lines 2-8; and in Example 2 as originally filed.

Applicant submits that these changes have added no new matter to the application or claims.

§112 Rejections of the Claims

Enablement

Claims 2, 4, 6, 8-10 and 22 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Specifically, the Examiner alleges that the specification does not

enable expressing a molecule on a cell, where the method involves photochemical internalization of a molecule sufficient to generate an immune response. The Examiner has separately stated that MHC II molecules are only expressed by antigen presenting cells. The Examiner also alleges that only certain photochemical internalization agents are enabled by the specification. This rejection is respectfully traversed.

The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

Claim 2 is directed to a method of presenting an antigenic peptide on the surface of a viable cancer cell, said method comprising: contacting said cancer cell with said antigenic peptide and with a photosensitizing agent, wherein said peptide and said agent are each taken up into an intracellular membrane-restricted compartment of said cell; irradiating said cell with light of a wavelength effective to activate the photosensitizing agent, such that the membrane of said intracellular compartment is disrupted, releasing said peptide into the cytosol of the cell, without killing the cell; wherein, said released antigenic peptide, or a part thereof of sufficient size to generate a cytotoxic T cell response, is subsequently presented on the surface of said cell by a class I MHC molecule; wherein presentation of the antigenic peptide, or part thereof, on the surface of said cell results in cytotoxic T cell mediated cell killing; and wherein the photosensitizing agent is selected from the group consisting of a porphyrin, phthalocyanine and a chlorin.

The Examiner admits that most cells do express MHC class I molecules, but doubts that MHC class II molecules are expressed on any cells other than antigen presenting cells. Reference to MHC class II molecules has been removed from claim 2, and claim 24 is drawn to antigen presenting cells. Moreover, claim 2 is drawn to presenting and antigenic peptide on the surface of a viable cancer cell, and is not drawn to all cell types. Also, rather than generating any type of immune response, claim 2 is directed to presentation of antigenic peptides on the surface of a cell by a class I MHC molecule, resulting in T lymphocyte mediated cell killing. In addition, claims 2 and 24 recite specific photosensitizing agents and are not drawn to all types of

photosensitizing agents. Accordingly, claims 2 and 24 are not so broad as the Examiner alleges and no undue experimentation is needed to practice the claimed invention.

The Examiner's attention is drawn to the following facts, which should alleviate any remaining doubt that the Examiner may have as to the presentation of antigenic peptides by MHC I molecules on various cell types and the presentation of antigenic peptides by MHC II molecules on antigen presenting cells.

First, the Examiner admits that the present photochemical methods can be used to internalize exogenous molecules (see Office Action last 3 lines of page 2, (Jan. 9, 2007)).

Second, as Examiner acknowledges, MHC I molecules are expressed on all cell types, and MHC II molecules are expressed on antigen presenting cells (Office Action, page 3, last paragraph). Confirmation of this fact is provided in the article entitled "Histocompatibility Molecules" (downloaded from the web on Oct. 9, 2006 from http://home.comcast.net/~john. kimball1/BiologyPages/H/HLA.html; submitted in the Supplemental Information Disclosure Statement filed Oct. 13, 2006), which also states that antigen presenting cells express both MHC I and II molecules (see page 4).

Third, the function of MHC molecules is to display antigens. As stated on page 3 of the "Histocompatibility Molecules" article, "Histocompatibility molecules present antigens to T cells."

Fourth, T cells mediate cell killing when they recognize a foreign antigen displayed by an MHC molecule on the surface of the cell. Applicant believes that the Examiner understands this point, but if there is any doubt, please refer to pages 880-881 of James D. Watson et al., MOLECULAR BIOLOGY OF THE GENE, 4th ed. (The Benjamin/Cummings Publishing Company, Inc. 1987; submitted in a Supplemental Information Disclosure Statement filed Oct. 13, 2006). As indicated on page 880, MHC proteins are present on the surface of all cell types in the body and cytotoxic T cells are able to eliminate any cell types, for example, that are infected with virus because those cells display viral antigens. In addition, the "Histocompatibility Molecules" article, further states that cytotoxic T cells contain the machinery for destroying cells whose MHC class I epitope they recognize.

Therefore, facts that cannot be denied are that the present methods lead to successful internalization of peptide antigens, MHC molecules can display foreign antigen on the surface of

cells, and cytotoxic T cells can kill cells when the cell recognizes a foreign antigen displayed on the surface of the cell.

What the Examiner appears to doubt is whether, once internalized, sufficient antigenic peptide is displayed by MHC molecules on the surface of cells.

However, Applicant has provided data showing that cell killing by cytotoxic T cells occurs only when the cytotoxic T cell recognizes the antigenic peptide on the surface of a cell. These data also demonstrate that methods of the invention achieve presentation of sufficient antigenic peptide to allow recognition and cytotoxic T cell mediated cell killing. In particular, Example 2 describes FM3 melanoma cells that were treated with the $AlPcS_{2a}$ photochemical internalization agent for 18 hours, then loaded with chromium and incubated with the MART-1 peptide for 5 hours. The chromium is taken up into the cells and used as a marker for cell lysis. After chromium uptake and incubation with the MART-1 peptide, the cells are washed to remove residual peptide, chromium, etc. Then, the cells are exposed to light (as indicated in FIG. 3). The cells are then incubated for eighteen hours to allow internalization and display of the MART-1 peptide on the FM3 melanoma cells. After this incubation, the melanoma cells are exposed for four hours to cytotoxic T cells that were specific for the MART-1 peptide, and then the amount of chromium in the released into the medium was measured as a marker of cell lysis. FIG. 3 shows that the percent cytotoxicity increases with increasing time of light exposure. When no light is used so that little or no photo-internalization of the MART-1 peptide occurs, little cell death is observed. However, increased light exposure leads to increased uptake and display of the MART-1 peptide which then leads to increased killing by the cytotoxic T cells.

These results mean that the MART-1 peptide is internalized and then presented on the cell's surface by Applicant's methods and the cytotoxic T cells then kill those cells that display the MART-1 peptide. No other conclusion can be drawn from this evidence. The Examiner has previously agreed and stipulated that Example 2 is enabled (Oct. 24, 2003 Office Action at page 2; Aug. 23, 2004 Office Action at page 4; April 1, 2005 Office Action at page 3). Accordingly, it cannot be denied that Example 2 demonstrates cell surface display of sufficient antigenic peptide to result in cytotoxic T cell mediated cell killing.

In addition, the Declaration by Anders Høgset (dated Nov. 13, 2002), provides further results demonstrating that the present methods produce cell surface expression. For example, in

his Declaration, Anders Høgset describes an experiment performed using the same procedures as those for Example 2, but with and without the MART-1 peptide. The results are shown in Figure 1 of the Declaration and summarized by Anders Høgset as follows:

> It will be seen from this Figure [1] that virtually no CTL-dependent killing occurs without the MART-1 peptide, regardless of whether the cells are illuminated or not. Addition of the MART-1 peptide induces a small level of cell killing (about 3.5%) without illumination, but illumination increases the cell killing substantially (about 4-fold in this experiment). In view of the selectively of CTL for MART-1 peptide appropriately processed and presented on the surface of the cell, this illustrates that photochemical treatment results in MART-1 internalization, processing and presentation on the surface of the cells in a form such that immune effector T cells are able to recognize and eliminate those cells.

Declaration under Rule 132 at page 2, by Anders Høgset (Nov. 13, 2002). Therefore, the cytotoxic T cells (CTLs) only kill substantial numbers of cells when the MART-1 peptide is present and the cell-peptide mixture is illuminated with light. These results can only be explained by light-induced uptake and display of the MART-1 peptide. Thus, the antigenic MART-1 peptide must be displayed on the surface of the cell.

These results are further confirmed by an understanding of the functions performed by cytotoxic T cells. As described in Watson et al. and "Histocompatibility Molecules," submitted herewith, cytotoxic T cell recognition and killing requires two things: MHC expression and a foreign antigen displayed on the surface of a cell. Without both the MHC and the displayed antigen, the cytotoxic T cell will not kill (e.g., lyse) the cell. Therefore, the melanoma cells of Example 2 *must* have displayed the MART-1 peptide (using MHC) or the MART-1-specific cytotoxic T cells would not have lysed these melanoma cells. No other conclusion is possible.

Accordingly, the evidence provided by Applicants does show that the methods of the invention lead to display of antigenic molecules on the surface of cells (e.g. melanoma cells).

The Examiner also states that the methods are unpredictable, alleging three things.

First, the Examiner alleges that the specification does not enable all toxic and non-toxic molecules. Applicant submits that the claims are drawn to presentation of non-toxic antigenic peptides. Thus, the claims are not so broad as the Examiner has alleged. One of skill in the art can readily perform the inventive methods using any such non-toxic antigenic peptides.

Second, the Examiner alleges that Figure 4 does not compel a conclusion that antigenic peptides are displayed on the surface of the cell. However, Figure 4 is not designed to show display of antigen. Instead, Figure 4 shows internalization of antigen as a function of exposure to light for zero to 120 seconds. Thus, Figure 4 shows that although the carcinoma cells are exposed to photosensitizing agent for significant time, little or no uptake of antigen (horseradish peroxidase, HRP) is observed in the cytosol until the cells are exposed to light (note that there is essentially no HRP activity in the cytosol at time zero in Figure 4). However, light exposure for as little as 30 seconds leads to about 50% cell uptake of HRP. Since the experiment was only conducted for 120 seconds, which is insufficient time for antigen display, one of skill in the art would not expect to see significant antigen display. (Note that in Example 2, cells were incubated for 18 hours after light exposure before exposure to cytotoxic T cells.) Moreover, upon internalization, proteolysis of the antigen can occur so that when displayed, the HRP would not be an intact molecule that can exhibit HRP activity (see, e.g., specification at page 11, lines 2-8). Figure 4 only identifies full size antigens because it examines HRP activity. Thus, Figure 4 does not show data inconsistent with the claimed invention.

Third, the Examiner quotes Inventor Høgset as allegedly disclosing factors not previously disclosed in the specification that are allegedly critical to the functionality of the claimed method. According to the Examiner, Inventor Høgset makes the following statements:

> "Whether of not cell death results after photochemical treatment is principally dependent on two factors. Firstly the amount of toxic substances generated by the photosensitizing compounds on exposure to light and secondly, the presence and toxicity of molecules which are internalized during this process."

Thus, the Examiner is apparently worried about toxicity. Applicants note that the claims are directed to presenting an antigenic peptide on the surface of a *viable* cancer cell. Claim 2 requires that irradiation of the cells and release of the antigenic peptide into the cell does not kill the cells. Hence, manipulation of dead cells should not be of concern.

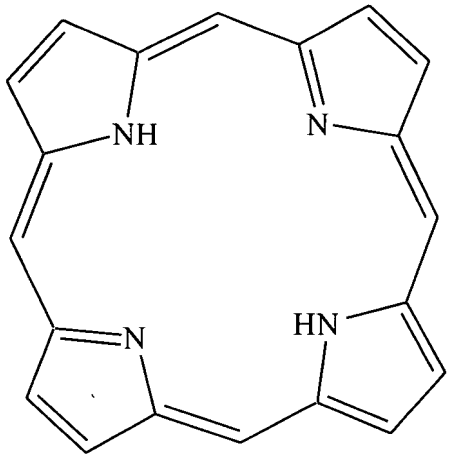
However, Applicant addresses the Examiner's concerns by first noting that Inventor Høgset continues in the Declaration to explain how these toxicity factors are controlled. In particular, the Examiner's attention is drawn to the two sentences that follow after the quote above:

> The level of toxic substances which are generated may be controlled by the selection of the photosensitizer to be used, the dose of that photosensitizer, but most crucially, the time of illumination which leads to increasing levels of the toxic substances. The second aspect, namely the toxicity resulting from the molecules which are introduced may be readily controlled by selecting an appropriate toxic or non-toxic molecule for transfer, depending on the desired end use. Declaration by Inventor Høgset at 2-3 (Nov. 2002)

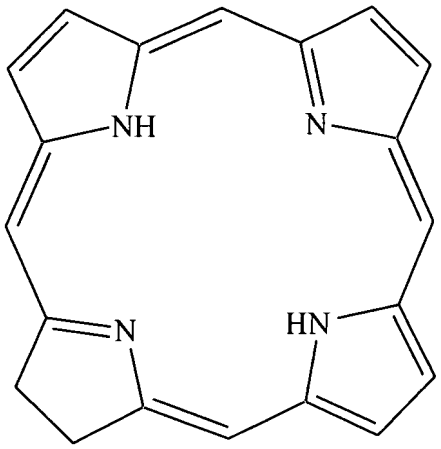
Thus, while two factors can give rise to toxicity (the process of photo-internalization and the molecule internalized), only the first source of toxicity is of concern for the present invention because the claims are directed to antigen display and killing cells by T cells (not cell killing by an internalized toxin).

Moreover, the claims are directed to well-tested photosensitizing agents whose properties during the photo-internalization process are well understood and can be controlled using the teachings of the present specification. Thus, one source of toxicity during the photo-internalization process is eliminated. In addition, Inventor Høgset explicitly explains how to avoid cell death during photo-internalization not only in the Examples of application (and at pages 14-15), but also by in the Declaration that shows what light dose avoids cell death. Thus, for example, as explicitly shown in Figure 2 of the Declaration, when internalizing non-toxic molecule, approximately 85% of cells survive a light dose lasting up to about 6 minutes, but longer light exposure results in greater cell death. Alternatively, shorter illumination times can be used to lead to even less cell death (see Declaration and Figure 2). Thus, given the teachings by the inventors in the specification as further exemplified the Declaration, one of skill in the art can readily avoid light doses that lead to cell death but are sufficient for internalization of non-toxic molecules.

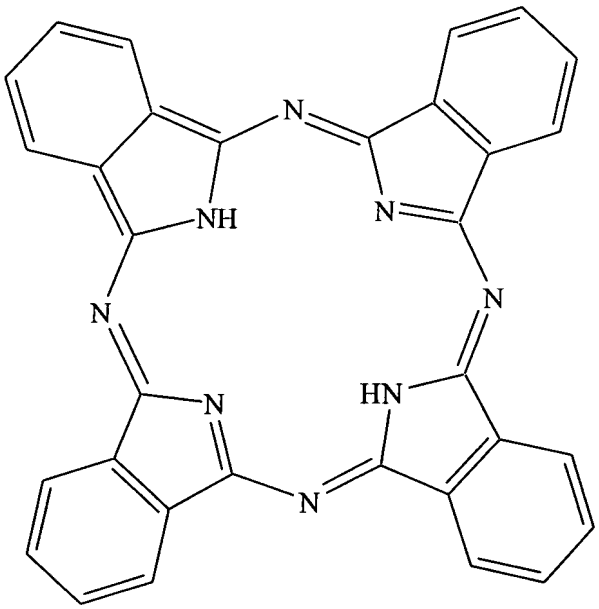
The well-tested photosensitizers of the claimed invention have structurally-related rings, as shown below.



Porphyrin



Chlorin



Phthalocyanine

Thus, the basic porphyrin ring differs from the chlorin ring by only one bond. The phthalocyanines are also closely related to porphyrins and chlorins in that the phthalocyanines are aza derivatives of tetrabenzoporphyrins. As such it is clear that these three classes are based on a common core structure (four linked pyrroles). Thus these three classes are members of a single, structurally and functionally related, genus. No undue experimentation is needed to practice the invention with these three types of photosensitizers.

The Examiner has also asserted that many cancer cells lose MHC I expression. However, the specification and Declaration specifically show antigenic peptide display on cancer cells. Even if some down-regulation of MHC I expression is occasionally observed, this is not a general phenomenon and such occasional down-regulation would not affect the performance of the invention. For example, Applicants enclose an article by Nijman et al. (Eur. J. Obstet. Gynecol. Reprod. Biol. 94: 114-20 (2001)). The Abstract of this article specifically states that "Downregulation of MHC class I on tumor cells was found in a minority of patients," and "The immune escape mechanism by MHC class I ... downregulation seems to be of minor importance." Furthermore, experiments performed in the specification (e.g., Example 2) use cancer cells (e.g., FM3 melanoma cells) and MHC Class I expression clearly still occurs in these cells. Thus, there is no evidence of record that MHC I down-regulation has any significant effect on the practice of the invention.

Accordingly, the facts, specification and evidence of record demonstrate that the claimed subject matter is fully enabled. Withdrawal of this rejection of claims 2, 4, 6, 8-10 and 22 under 35 U.S.C. § 112, first paragraph is respectfully requested.

Written Description

To satisfy the written description requirement, Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he was in possession of the invention, and that the invention, in that context, is whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991), and see M.P.E.P. § 2163.02.

The Examiner has made two written description rejections, which are separately discussed below.

First, claims 2, 4, 6, 8-10, 22 and 24-29 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description of a porphyrin, phthalocyanine, purpurin, chlorin, benzoporphyrin, naphthalocyanine, cationic dye, or tetracycline at the time of filing.

Applicant assumes that rejection of claim 24, and claims dependent thereon, is an error, because claim 24 is drawn to specific photosensitizing agents. Clarification is requested.

Claim 2 is directed to particular well-defined photosensitizing agents selected from the group consisting of a porphyrin, a phthalocyanine and a chlorin. Claim 22 has been cancelled without prejudice to its prosecution in another application.

Applicant submits that one of skill in the art would understand that the inventors were in possession of the porphyrin, phthalocyanine and chlorin photosensitizing agents at the time of filing the present application because these types of agents are described and employed in the experiments explained in the Examples. Thus, one of skill in the art can have no doubt as to the possession of these agents by Applicants at the time of filing.

Withdrawal of this rejection of claims 2, 4, 6, 8-10, 22 24-29 under 35 U.S.C. § 112, first paragraph, with respect to the written description of the photosensitizing agents is respectfully requested.

Second, claims 2, 4, 6, 8-10, 22 and 24-29 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description of an antigenic molecule presented on the surface of a cell by an MHC class II molecule. According to the Examiner, page 10 of the specification discloses peptide-MHC class II complexes at the surface of a treated cell, but does not disclose all antigenic molecules presented at a treated cell surface.

Claim 2 is now drawn to MHC I presentation of peptide antigens (not MHC II presentation of antigenic molecules) and claim 22 is drawn to MHC II presentation of peptide antigens on antigen presenting cells.

Applicant submits that as admitted by the Examiner on page 8 of the Office Action, the specification provides a written description of peptides MHC class II complexes at the surface of antigen presenting cells using the methods of the invention. Moreover, the specification does disclose presentation of a variety of antigenic peptides, for example, in the Examples and at page 6, lines 33 to page 8, line 30 (see especially, page 7, line 16 to page 8, line 30).

Accordingly, withdrawal of this rejection of claims 2, 4, 6, 8-10, 22, 24-29 under 35 U.S.C. § 112, first paragraph, with respect to the written description of the MHC type is respectfully requested.

§102 Rejection of the Claims

Claims 2, 4, 6, 8-10, and 22 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by PCT Application Publication No. WO96/07432 by Berg. The Examiner alleges that WO96/07432 inherently anticipates the invention.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ 2d 1913, 1920 (Fed. Cir. 1989). To constitute anticipation, the claimed subject matter must be identically disclosed in the prior art. *In re Arkley*, 172 U.S.P.Q. 524 at 526 (C.C.P.A. 1972). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 101 (Fed. Cir. 1991). To overcome the defense of anticipation, "it is only necessary for the patentee to show some tangible difference between the invention and the prior art." *Del Mar Engineering Lab v. Physio-Tronics, Inc.*, 642 F.2d 1167, 1172, (9th Cir. 1981).

Moreover, an anticipation rejection that is based on inherency must be supported by factual and technical grounds establishing that the inherent feature must flow as a necessary conclusion, not simply a possible conclusion, from the teaching of the cited art. *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Int. 1990); *In re Oelrich*, 666 F.2d 578, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

Applicant submits that WO96/07432 does not disclose or teach every element of the claimed invention. For example, at a minimum, WO96/07432 does not disclose or teach the following three elements: 1) transfer of antigenic peptides into the cell; 2) antigenic peptide presentation on the surface of the cell; and 3) cytotoxic T cell mediated cell killing.

Applicant submits that even if WO96/07432 discloses transfer of whole molecules into the cytosol of cells, WO96/07432 does not disclose, or provide any reason for, transferring *antigenic peptides* into a cell. For example, the terms "antigen" and "antigenic" do not appear in the WO96/07432 disclosure. Similarly, one of skill in the art would not be motivated by the WO96/07432 disclosure to introduce antigens and antigenic peptides into a cell because there is

no recognition that the cell receiving the molecule can be involved in an immune response. Thus, WO96/07432 disclosure makes no mention of the terms "immune," "immunological," "cytotoxic T cell" and "CTL." Thus, there is no disclosure or recognition in the WO96/07432 disclosure that antigenic peptide can or should be transferred into cells to generate a cytotoxic T cell response.

In contrast to the present invention, the WO96/07432 disclosure is limited to whole molecules that may kill or otherwise directly affect the cell into which they are transferred. One of skill in the art would not be motivated by WO96/07432 to transfer a peptide that has no enzymatic function, no toxicity and performs no function other than being antigenic into a cell because WO96/07432 fails to make the connection between stimulating a T cell response against the cell by transferring antigens into the cell. Thus, while WO96/07432 mentions the term "polypeptide" only once, in the context of describing a molecule that serves as a toxin, WO96/07432 does not disclose the term "peptide" anywhere in the disclosure. Such failure reflects the fact that WO96/07432 only discloses transfer of whole molecules into cells and does not recognize or contemplate transfer of non-toxic peptides with no enzymatic or inhibitory functions other than being antigenic. Accordingly, the WO96/07432 disclosure fails to disclose the element relating to contacting a cell with an antigenic peptide and presenting an antigenic peptide on the surface of cells.

In summary, the following words do not appear anywhere in the WO96/07432 disclosure:

a) "presenting"
b) "presentation"
c) "display"
d) "antigen"
e) "antigenic" with or without "peptide"
f) "immune"
g) "immunological"
h) "cytotoxic T cell"
i) "major"
j) "histocompatibility"
k) "MHC"

l) "type I"

m) "type II"

With respect to the Examiner's allegations regarding inherent anticipation, Applicant reminds the Examiner that even if WO96/07432 discloses transfer of molecules into the cytosol of cells, new uses of such molecules (and especially of antigenic peptides not disclosed in the cited art) are indeed patentable subject matter. *See* 35 U.S.C. § 101 (identifying as patentable "any new and useful improvements" of a process, machine, manufacture, etc.); *Perricone v. Medicus Pharmaceutical Corp.* 432 F.3d. 1368, 1378-79, 77 U.S.P.Q.2d 1321 (Fed. Cir. 2005); *In re King*, 801 F.2d 1324, 1326 (Fed. Cir. 1986) (principles of inherency do not prohibit a process patent for a new use of an old structure).

As the Federal Circuit stated in the *Perricone v. Medicus* case:

> Claim 1 of the '693 patent recites a new use of the composition disclosed by Pereira, i.e., the treatment of skin sunburn. The district court's inherent anticipation analysis for this claim contains a flaw. The disclosed use of Pereira's lotion, i.e., topical application, does not suggest application of Pereira's lotion to skin sunburn. In other words, the district court's inherency analysis goes astray because it assumes what Pereira neither disclosed nor rendered inherent. Because Pereira does not disclose topical application to skin sunburn, this court reverses the district court's holding that Pereira anticipates claims 1-4 and 7 of the '693 patent.

432 F.3d. 1368, 1378-79. Applicant submits that this principle governs in this case as well.

Thus, just as the Federal Circuit found in the *Perricone v. Medicus* case that topical application of a known composition does not inherently anticipate methods of treating skin sunburn with that composition, so to does disclosure of methods of transferring molecules into the cytosol of cells by WO96/07432 fail to inherently disclose Applicant's methods of presenting antigenic peptides on the surface of cancer cells to generate a cytotoxic T cell response.

Moreover, as described above, an anticipation rejection that is based on inherency must be supported by factual and technical grounds establishing that the inherent feature must flow as a necessary conclusion, not simply a possible conclusion, from the teaching of the cited art.

Applicant submits that WO96/07432 does not provide factual grounds establishing that antigen presentation and stimulation of an immune response necessarily occurs. In particular, the specification discloses nothing about generating an immune response ("immune" and

"immunological" appear nowhere) and each of the twelve examples recited in WO96/07432 utilizes a cytotoxin to kill the cells that internalize the cytotoxin. Thus, one of skill in the art could not conclude that any molecule transferred into the cells pursuant to WO96/07432 will necessarily generate a cytotoxic T cell response because WO96/07432 is silent on this issue and the WO96/07432 Examples all produce dead or dying cells. Dead and dying cells cannot move an antigenic peptide from the cytosol to the cell surface and thereby generate a cytotoxic T cell response.

Indeed, in any cancer treatment even contemplated in accordance with the teaching of WO96/07432, it would be assumed that the cancer cells would need to be killed by aggressive photodynamic therapy or by the internalized molecule as the authors at that time were unaware that an internalized molecule could be presented on the cell surface which would then allow the generation of a CTL response. The only molecule that would therefore be selected for internalization would be one having an immediate and direct effect on the viability of the cells, i.e. a toxic molecule. In contrast, the methods as claimed require that display occurs on the surface of a viable cell and that the cell is not killed after irradiation and internalization of the antigenic peptide.

Accordingly, WO96/07432 neither explicitly nor inherently anticipates the subject matter of the claimed invention. Applicant requests withdrawal of this rejection of claims 2, 4, 6, 8-10 and 22 under 35 U.S.C. § 102(b).

Conclusion

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: MS Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 9th day of July, 2007.

PATRICIA A. HULTMAN

Name

Signature